5

Abstract

This invention is directed to the use of diaryl acid derivatives of formula (I) and their pharmaceutical compositions as PPAR ligand receptor binders. The PPAR ligand receptor binders of this invention are useful as agonists or antagonists of the PPAR receptor

wherein: $\begin{array}{c|c}
R_1 & R_3 & R_5 & R_7 \\
R_2 & R_4 & R_4 & R_6 & R_8
\end{array}$ wherein:

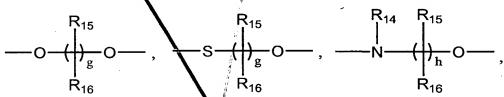
Ar II Ar II

and are independently aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused

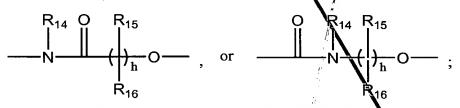
arylheterocyclenyl, fused arylheterocyclyl, heteroaryl, fused heteroarylcycloalkenyl, fused

heteroarylcycloalkyl, fused heteroarylheterocyclenyl, or fused heteroarylheterocyclyl;

A is -O-, -S-, -SO-, -SO₂-, -NR₁₃-, -C(O), -N(R₁₄)C(O)-, -C(O)N(R₁₅)-, -N(R₁₄)C(O)N(R₁₅)-, -C(R₁₄)=N-,



a chemical bond,



B is –O-, -S-, -NR₁₉-, a chemical bond, -C(O)-, -N(R₂₀)C(O)-, or –C(O)N(R₂₀)-;

- 15 E is a chemical bond or an ethylene group;
 - a is 0-6;
 - b is 0-4;
 - c is 0-4;
 - d is 0-6;
- 20 g is 1-5;
 - h is 1-4;

 R_1 , R_3 , R_5 and R_7 , are independently hydrogen, halogen, alkyl, carboxyl, alkoxycarbonyl or aralkyl; R_2 , R_4 , R_6 and R_8 , are independently -(CH₂)_q-X;

q is 0-3;

X is hydrogen, halogen, alkyl, alkenyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, alkoxy, aralkoxy, heteroaralkoxy, carboxyl, alkoxycarbonyl, tetrazolyl, acyl, acylHNSO₂-, - SR₂₃, Y¹YN- or Y³Y⁴NCO-;

 Y^1 and Y^2 are independently hydrogen, alkyl, aryl, aralkyl or heteroaralkyl, or one of Y^1 and Y^2 is

bydrogen or alkyl and the other of Y¹ and Y² is acyl or aroyl;

Y³ and Y⁴ are independently hydrogen, alkyl, aryl, aralkyl or heteroaralkyl;

Z is R₂₁O₂C₇, R₂₁OC₇ cyclo-imide. -CN, R₂₁O₂SHNCO₇ R₂₁O₂SHN₇ (R₂₁)₂N

Z is R₂₁O₂C-, R₂₁OC-, cyclo-imide, -CN, R₂₁O₂SHNCO-, R₂₁O₂SHN-, (R₂₁)₂NCO-, R₂₁O- 2,4-

thiazolidinedionyl, or tetrazolyl; and

R₁₉ and R₂₁ are independently hydrogen, alkyl, aryl, cycloalkyl, or aralkyl;

10 R₁₃, R₁₇, R₁₉ and R₂₃ are independently R₂₂OC-, R₂₂NHOC-, hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, heteroaralkyl, or aralkyl,

 R_{14} , R_{15} , R_{16} , R_{18} and R_{20} are independently hydrogen, alkyl, aralkyl, carbonyl, or alkoxycarbonyl; or R_{14} , and R_{15} taken together with the carbon and nitrogen atoms through which they are linked form a 5 or 6-membered azaheterocyclyl group; or

when a is 2-6, then at least one pair of vicinal R₁ radicals taken together with the carbon atoms to which

R₂ group; or

the R₁ radicals are linked form a

when b is 2-4, then at least one pair of vicinal R₃ radicals taken together with the carbon atoms to which

R₄ group; or

the R₃ radicals are linked form a

when c is 2-4, then at least one pair of vicinal R5 radicals taken together with the carbon atoms to which

Re The Re

20 the R₅ radicals are linked form a

group; or

when d is 2-6, then at least one pair of vicinal R₇ radicals taken together with the carbon atoms to which

R₈

the R7 radicals are linked form a

R₈ group, or a 5-membered cycloalkyl group, or

when d is 2-6, then at least one pair of non-vicinal R₇ radicals taken together with the carbon atoms to which the R₇ radicals are linked form a 5-membered cycloalkyl group; or

geminal R₅ and R₆ radicals taken together with the carbon atom through which these radicals are linked form a 5 membered cycloalkyl group; or

geminal R₇ and R₈ radicals taken together with the carbon atom through which these radicals are linked form a 5 membered cycloalkyl group; and

R₂₂ is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, heteroaralkyl, or aralkyl; or a pharmaceutically acceptable salt thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

Cold)

5